CLAIMS

1. A method of treating systemic lupus erythematosus in a patient which comprises administering to the patient a systemic lupus erythematosus treating effective amount of a growth hormone secretagogue (GHS), a prodrug thereof or a pharmaceutically acceptable salt of said GHS or of said prodrug.

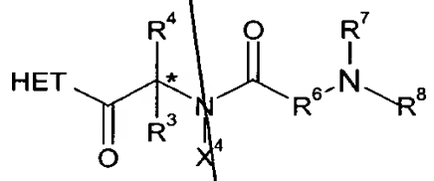
2. A method of claim 1 wherein the GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug is an orally active GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug.

3. A method of claim 2 wherein the GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug is orally administered.

4. A method of claim 1 wherein the GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug is a non-peptidyl GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug.

5. A method of claim 1 wherein the patient is a human.

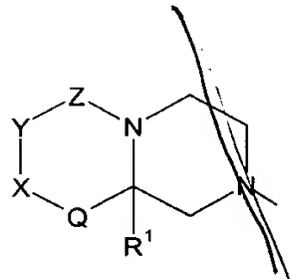
6. A method of claim 4 wherein said GHS is a compound of the Formula I:



or a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer thereof, or a prodrug of such compound, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug,

wherein:

HET is a heterocyclic moiety selected from the group consisting of



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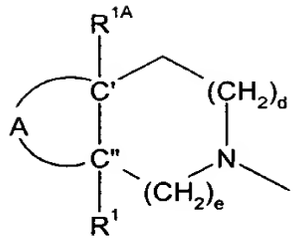

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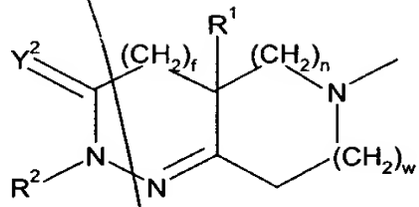

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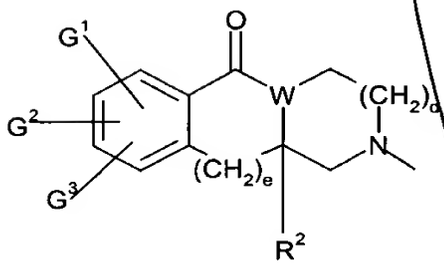

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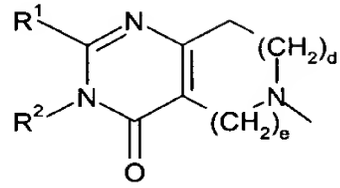


d is 0, 1 or 2;

e is 1 or 2;

f is 0 or 1;

n and w are 0, 1 or 2, provided that n and w cannot both be 0 at the same time;

Y^2 is oxygen or sulfur;

A is a divalent radical, where the left hand side of the radical as shown below is connected to C" and the right hand side of the radical as shown below is connected to C', selected from the group consisting of

$-NR^2-C(O)-NR^2-$, $-NR^2-S(O)_2-NR^2-$, $-O-C(O)-NR^2-$, $-NR^2-C(O)-O-$, $-C(O)-NR^2-C(O)-$, $-C(O)-NR^2-C(R^9R^{10})-$, $-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-O-C(O)-$, $-C(R^9R^{10})-O-C(R^9R^{10})-$, $-NR^2-C(O)-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-$, $-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(O)-O-$, $-C(O)-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-O-C(O)-$, $-NR^2-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-$, $-C(R^9R^{10})-NR^2-C(O)-O-$, $-C(R^9R^{10})-O-C(O)-NR^2-$,

$-C(R^9R^{10})-NR^2-C(O)-NR^2-$, $-NR^2-C(O)-O-C(R^9R^{10})-$, $-NR^2-C(O)-NR^2-C(R^9R^{10})-$, $-NR^2-S(O)_2-NR^2-C(R^9R^{10})-$, $-O-C(O)-NR^2-C(R^9R^{10})-$, $-C(O)-N=C(R^{11})-NR^2-$, $-C(O)-NR^2-C(R^{11})=N-$, $-C(R^9R^{10})-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-C(R^{11})=N-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-N(R^{12})-$, $-C(R^9R^{10})-NR^{12}-$, $-N=C(R^{11})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-S(O)_2-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-O-$, $-C(R^9R^{10})-S(O)_2-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-$, $-O-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-O-$, $-C(R^9R^{10})-C(O)-C(R^9R^{10})-$, $-C(O)-C(R^9R^{10})-C(R^9R^{10})-$ and $-C(R^9R^{10})-NR^2-S(O)_2-NR^2-$;

Q is a covalent bond or CH_2;

W is CH or N;

X is CR^9R^{10}, $C=CH_2$ or C=O;

Y is CR^9R^{10}, O or NR^2;

Z is C=O, C=S or $S(O)_2$;

G^1 is hydrogen, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, $-CONH_2$, $-(C_1-C_4)$alkyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkoxy optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkylthio, phenoxy, $-COO(C_1-C_4)$alkyl, N,N-di-(C_1-C_4)alkylamino, $-(C_2-C_6)$alkenyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_2-C_6)$alkynyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_3-C_6)$cycloalkyl optionally independently substituted with one or more (C_1-C_4)alkyl groups, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkylamino carbonyl or di-(C_1-C_4)alkylamino carbonyl;

G^2 and G^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, $-(C_1-C_4)$alkyl optionally independently substituted with one to three halo groups and $-(C_1-C_4)$alkoxy optionally independently substituted with one to three halo groups;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)S(O)_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)S(O)_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$,

$-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)S(O)_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6-$, $-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro groups or 1 or 2 (C_1-C_4)alkyl groups;

R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, (C_1-C_6)alkyl, phenyl(C_1-C_3)alkyl, pyridyl(C_1-C_3)alkyl, thiazolyl(C_1-C_3)alkyl and thienyl(C_1-C_3)alkyl, provided that R^{1A} is not F, Cl, Br or I when a heteroatom is vicinal to C";

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxy, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 independently selected halo groups;

R^3 is selected from the group consisting of A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl, $-(C_1-C_5)$alkyl-$X^1-(C_0-C_5)$alkyl-A^1 and $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl-(C_3-C_7)cycloalkyl;

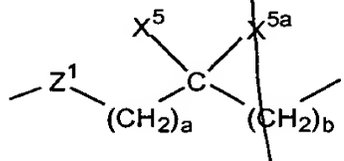
where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 independently selected halo groups or 1, 2 or 3 independently selected $-OX^3$ groups;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7)cycloalkyl, $(C_5-$

C_7)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or $(C_1$-$C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are each independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3, A^1 and optionally substituted $(C_1$-$C_6)$alkyl;

the optionally substituted $(C_1$-$C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1$-$C_6)$alkyl, $-C(O)OX^2$, $(C_3$-$C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

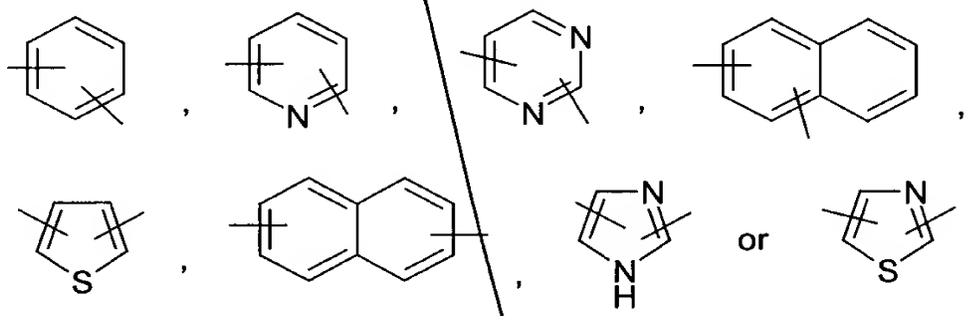
or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or

fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

or R^6 is -$(CR^aR^b)_a$-E-$(CR^aR^b)_b$-, where the -$(CR^aR^b)_a$- group is attached to the carbonyl carbon of the amide group of the compound of formula I and the -$(CR^aR^b)_b$ group is attached to the terminal nitrogen atom of the compound of formula I;

E is -O-, -S-, -CH=CH- or an aromatic moiety selected from



said aromatic moiety in the definition of E optionally substituted with up to three halo, hydroxy, -N(R^c)(R^c), (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

R^a and R^b are, for each occurrence, independently hydrogen, (C_1-C_6)alkyl, trifluoromethyl, phenyl or monosubstituted (C_1-C_6)alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR^c, $S(O)_mR^c$, $C(O)OR^c$, (C_3-C_7)cycloalkyl, -N(R^c)(R^c), -$C(O)N(R^c)(R^c)$, or R^a or R^b may independently be joined to one or both of R^7 or E (where E is other than O, S or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^a or R^b and the R^7 or E group, wherein the bridge contains 1 to 8 carbon atoms; or R^a and R^b may be joined to one another to form a (C_3-C_7)cycloalkyl;

R^c, for each occurrence, is independently hydrogen or (C_1-C_6)alkyl;

a and b are independently 0, 1, 2 or 3, with the proviso that if E is -O- or -S-, b is other than 0 or 1 and with the further proviso that if E is -CH=CH-, b is other than 0;

R^7 and R^8 are each independently hydrogen or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O-(C_1-C_6)$alkyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 $-O-C(O)(C_1-C_{10})$alkyl groups or 1 to 3 (C_1-C_6)alkoxy groups; or

R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, fluoro, hydroxy and (C_1-C_5)alkyl optionally independently substituted with 1-5 halo groups;

R^{11} is selected from the group consisting of (C_1-C_5)alkyl and phenyl optionally substituted with 1-3 substitutents each independently selected from the group consisting of (C_1-C_5)alkyl, halo and (C_1-C_5)alkoxy;

R^{12} is selected from the group consisting of (C_1-C_5)alkylsulfonyl, (C_1-C_5)alkanoyl and (C_1-C_5)alkyl where the alkyl portion is optionally independently substituted by 1-5 halo groups;

A^1 for each occurrence is independently selected from the group consisting of (C_5-C_7)cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-S(O)_2N(X^6)(X^6)$, $-N(X^6)S(O)_2$-phenyl, $-N(X^6)S(O)_2X^6$, $-CONX^{11}X^{12}$, $-S(O)_2NX^{11}X^{12}$,

$-NX^6S(O)_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6S(O)_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $-S(O)_m(C_1\text{-}C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 $(C_1\text{-}C_{10})$alkanoyloxy groups or 1 to 3 $(C_1\text{-}C_6)$alkoxy groups;

X^{12} is hydrogen, $(C_1\text{-}C_6)$alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, the X^{12} group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r\text{-}L^1\text{-}(CH_2)_r$-;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted $(C_1\text{-}C_6)$alkyl or optionally substituted $(C_3\text{-}C_7)$cycloalkyl, where the optionally substituted $(C_1\text{-}C_6)$alkyl and optionally substituted $(C_3\text{-}C_7)$cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halo groups or 1-3 OX^3 groups;

X^3 for each occurrence is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$halogenated alkyl, optionally substituted $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$-halogenated cycloalkyl, where optionally substituted $(C_1\text{-}C_6)$alkyl and optionally substituted $(C_3\text{-}C_7)$cycloalkyl in the definition of X^6 is optionally independently mono- or di-substituted with $(C_1\text{-}C_4)$alkyl, hydroxy, $(C_1\text{-}C_4)$alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1\text{-}C_6)$alkyl, carboxylate $(C_1\text{-}C_4)$alkyl ester or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently $(C_1\text{-}C_6)$alkyl, the two $(C_1\text{-}C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 as a ring member;

X^7 is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with hydroxy;

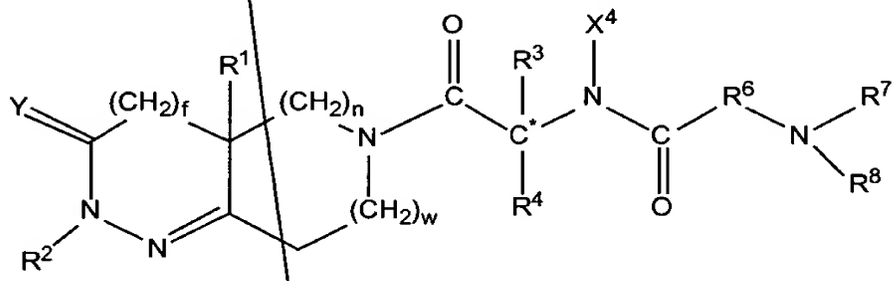
m for each occurrence is independently 0, 1 or 2;

with the provisos that:

1) X^6 and X^{12} cannot be hydrogen when attached to C(O) or $S(O)_2$ in the form $C(O)X^6$, $C(O)X^{12}$, $S(O)_2X^6$ or $S(O)_2X^{12}$; and

2) when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r$-L-$(CH_2)_r$- is independently 2 or 3.

7. A method of claim 6 wherein said GHS is a compound of the formula



a racemic-diastereomeric mixture or optical isomer of said compound or a pharmaceutically-acceptable salt or prodrug thereof,

wherein

f is 0;

n is 0 and w is 2, or n is 1 and w is 1, or n is 2 and w is 0;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t$-A^1, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t$-A^1, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t$-A^1, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t$-A^1, $-(C_1$-$C_{10})$alkyl, $-(CH_2)_t$-A^1, $-(CH_2)_q$-$(C_3$-$C_7)$cycloalkyl, $-(CH_2)_q$-Y^1-$(C_1$-$C_6)$alkyl, $-(CH_2)_q$-Y^1-$(CH_2)_t$-A^1 or $-(CH_2)_q$-Y^1-$(CH_2)_t$-$(C_3$-$C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(C_1$-$C_4)$alkyl, hydroxyl, $(C_1$-$C_4)$alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1$-$C_6)$alkyl, $-CO_2(C_1$-$C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$-, -CH=CH-, -C≡C-, $-N(X^6)C(O)$-, $-C(O)NX^6$-, -C(O)O-, $-OC(O)N(X^6)$- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, $(C_1\text{-}C_4)$alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-CO_2(C_1\text{-}C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 $(C_1\text{-}C_4)$alkyl;

R^2 is hydrogen, $(C_1\text{-}C_8)$alkyl, $-(C_0\text{-}C_3)$alkyl-$(C_3\text{-}C_8)$cycloalkyl, $-(C_1\text{-}C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 halogen;

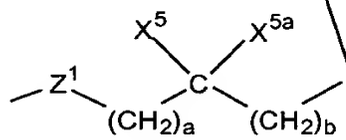
R^3 is A^1, $(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_6)$alkyl-A^1, $-(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_0\text{-}C_5)$alkyl-A^1 or $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl-$(C_3\text{-}C_7)$cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_7)$cycloalkyl;

X^4 is hydrogen or $(C_1\text{-}C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^2$, $(C_3\text{-}C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

R^7 and R^8 are independently hydrogen or optionally substituted $(C_1\text{-}C_6)$alkyl;

where the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O\text{-}(C_1\text{-}C_6)$alkyl, $-S(O)_m(C_1\text{-}C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O\text{-}C(O)(C_1\text{-}C_{10})$alkyl or 1 to 3 $(C_1\text{-}C_6)$alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r\text{-}L\text{-}(CH_2)_r-$;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 in the definition of R^1 is a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 in the definition of R^2, R^3, R^6, R^7 and R^8 is independently $(C_5\text{-}C_7)$cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8- membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitorgen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, $(C_1\text{-}C_6)$alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1\text{-}C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl or tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

where L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, carboxylate (C_1-C_4)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

8. A method of claim 7 wherein the GHS is 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

9. A method of claim 8 wherein the GHS is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, L-tartrate.

10. A method of claim 7 wherein the GHS is 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

11. A method of claim 10 wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide.

12. A method of claim 7 wherein the GHS is 2-amino-N-{1(R)-benzyloxymethyl-2-[1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

13. A method of claim 12 wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl)-2-methyl-propionamide.

14. A method of claim 1 which further comprises administering a recombinant growth hormone or an additional GHS selected from the group consisting of GHRP-6, GHRP-1, GHRP-2, growth hormone releasing factor and an analog of growth hormone releasing factor.

15. A method of claim 1 which further comprises administering methotrexate, dapsone, a glucocorticoid or an antimalarial, a prodrug of methotrexate, dapsone, a glucocorticoid or an antimalarial or pharmaceutically acceptable salt thereof or of said prodrug.

Sub B1 Cont

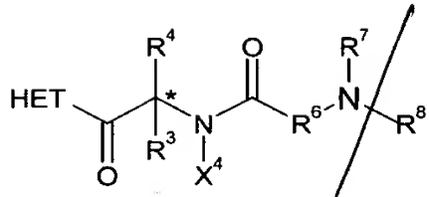
16. A method of claim 15 wherein said glucocorticoid is prednisone, betamethasone dipropionate, clobetasol, diflorasone diacetate, halobetasol propionate, amcinonide, desoximetasone, fluocinonide, halcinonide, betamethasone valerate, triamcinolone acetate, fluocinolone acetonide, flurandrenolide, hydrocortisone valerate, triamcinolone acetonide, hydrocortisone butyrate, alclometasone dipropionate, desonide, mometasone furoate, dexamethasone, hydrocortisone or methylprednisolone acetate.

17. A method of claim 15 wherein said antimalarial is chloroquine, hydroxychloroquine, quinacrine or quinine.

18. A combination comprising a GHS, a prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug and a second therapeutic agent selected from methotrexate, dapsone, a glucocorticoid or an antimalarial, a prodrug of said agent or a pharmaceutically acceptable salt thereof or of said prodrug.

19. A pharmaceutical composition comprising a combination of claim 18 and a pharmaceutically acceptable carrier, vehicle or diluent.

20. A combination of claim 18 wherein said GHS is a compound of the Formula I:



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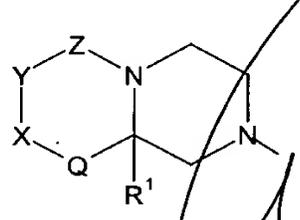
or a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer thereof, or a prodrug of such compound, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug,

wherein:

HET is a heterocyclic moiety selected from the group consisting of



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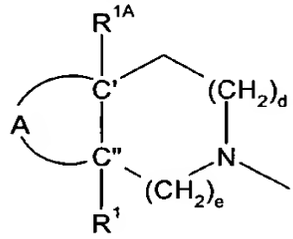

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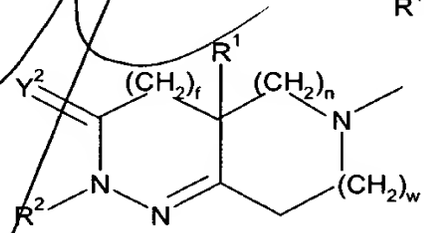

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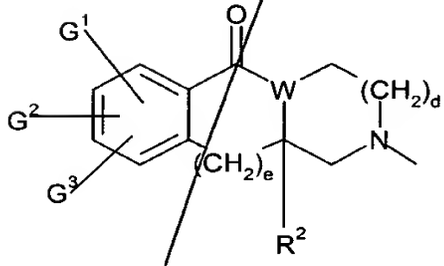

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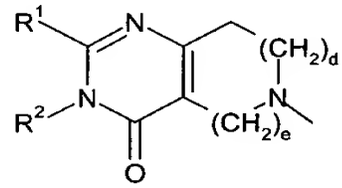


d is 0, 1 or 2;

e is 1 or 2;

f is 0 or 1;

n and w are 0, 1 or 2, provided that n and w cannot both be 0 at the same time;

Y^2 is oxygen or sulfur;

A is a divalent radical, where the left hand side of the radical as shown below is connected to C" and the right hand side of the radical as shown below is connected to C', selected from the group consisting of

$-NR^2-C(O)-NR^2-$, $-NR^2-S(O)_2-NR^2-$, $-O-C(O)-NR^2-$, $-NR^2-C(O)-O-$, $-C(O)-NR^2-C(O)-$, $-C(O)-NR^2-C(R^9R^{10})-$, $-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-O-C(O)-$, $-C(R^9R^{10})-O-C(R^9R^{10})-$, $-NR^2-C(O)-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-$, $-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(O)-O-$, $-C(O)-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-O-C(O)-$, $-NR^2-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-$, $-C(R^9R^{10})-NR^2-C(O)-O-$, $-C(R^9R^{10})-O-C(O)-NR^2$, $-C(R^9R^{10})-NR^2-C(O)-NR^2-$, $-NR^2-C(O)-O-C(R^9R^{10})-$, $-NR^2-C(O)-NR^2-C(R^9R^{10})-$, $-NR^2-S(O)_2-NR^2-C(R^9R^{10})-$, $-O-C(O)-NR^2-C(R^9R^{10})-$, $-C(O)-N=C(R^{11})-NR^2-$, $-C(O)-NR^2-C(R^{11})=N-$, $-C(R^9R^{10})-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-C(R^{11})=N-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-N(R^{12})-$, $-C(R^9R^{10})-NR^{12}-$, $-N=C(R^{11})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-S(O)_2-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-O-$, $-C(R^9R^{10})-S(O)_2-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-$, $-O-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-O-$, $-C(R^9R^{10})-C(O)-C(R^9R^{10})-$, $-C(O)-C(R^9R^{10})-C(R^9R^{10})-$ and $-C(R^9R^{10})-NR^2-S(O)_2-NR^2-$;

Q is a covalent bond or CH_2;

W is CH or N;

X is CR^9R^{10}, $C=CH_2$ or C=O;

Y is CR^9R^{10}, O or NR^2;

Z is C=O, C=S or $S(O)_2$;

G^1 is hydrogen, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, $-CONH_2$, $-(C_1-C_4)$alkyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkoxy optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkylthio, phenoxy, $-COO(C_1-C_4)$alkyl, N,N-di-(C_1-C_4)alkylamino, $-(C_2-C_6)$alkenyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_2-C_6)$alkynyl optionally independently

substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, -(C_3-C_6)cycloalkyl optionally independently substituted with one or more (C_1-C_4)alkyl groups, one or more halogens or one or more hydroxy groups, -(C_1-C_4)alkylamino carbonyl or di-(C_1-C_4)alkylamino carbonyl;

G^2 and G^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, -(C_1-C_4)alkyl optionally independently substituted with one to three halo groups and -(C_1-C_4)alkoxy optionally independently substituted with one to three halo groups;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)S(O)_2(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)S(O)_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t$-A^1, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t$-A^1, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t$-A^1, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)S(O)_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t$-A^1, -(C_1-C_{10})alkyl, $-(CH_2)_t$-A^1, $-(CH_2)_q$-(C_3-C_7)cycloalkyl, $-(CH_2)_q$-Y^1-(C_1-C_6)alkyl, $-(CH_2)_q$-Y^1-$(CH_2)_t$-A^1 or $-(CH_2)_q$-Y^1-$(CH_2)_t$-(C_3-C_7)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$-, -CH=CH-, -C≡C-, $-N(X^6)C(O)$-, $-C(O)NX^6$-, -C(O)O-, $-OC(O)N(X^6)$- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro groups or 1 or 2 (C_1-C_4)alkyl groups;

R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, (C_1-C_6)alkyl, phenyl(C_1-C_3)alkyl, pyridyl(C_1-C_3)alkyl, thiazolyl(C_1-C_3)alkyl and thienyl(C_1-C_3)alkyl, provided that R^{1A} is not F, Cl, Br or I when a heteroatom is vicinal to C";

R^2 is hydrogen, (C_1-C_8)alkyl, -(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl, -(C_1-C_4)alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxy, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 independently selected halo groups;

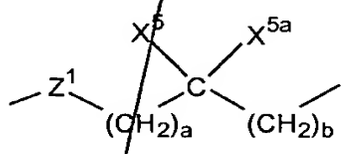
R^3 is selected from the group consisting of A^1, $(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_6)$alkyl-A^1, $-(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_0\text{-}C_5)$alkyl-A^1 and $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl-$(C_3\text{-}C_7)$cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 independently selected halo groups or 1, 2 or 3 independently selected $-OX^3$ groups;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_7)$cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form $(C_5\text{-}C_7)$cycloalkyl, $(C_5\text{-}C_7)$cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or $(C_1\text{-}C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are each independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3, A^1 and optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^2$, $(C_3\text{-}C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

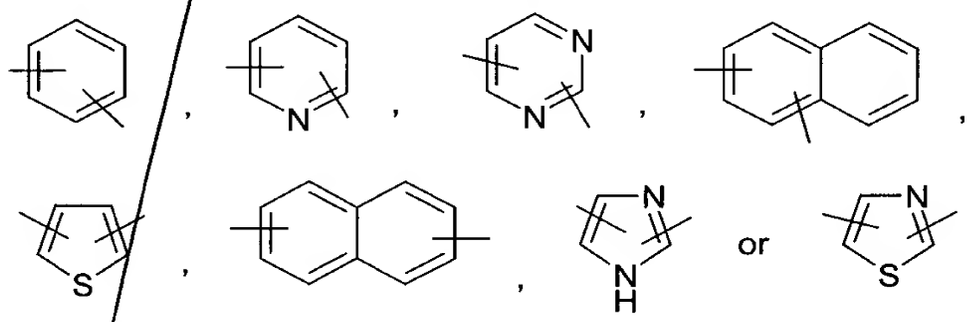
or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

or R^6 is $-(CR^aR^b)_a-E-(CR^aR^b)_b-$, where the $-(CR^aR^b)_a-$ group is attached to the carbonyl carbon of the amide group of the compound of formula I and the $-(CR^aR^b)_b$ group is attached to the terminal nitrogen atom of the compound of formula I;

E is -O-, -S-, -CH=CH- or an aromatic moiety selected from



said aromatic moiety in the definition of E optionally substituted with up to three halo, hydroxy, $-N(R^c)(R^c)$, (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

R^a and R^b are, for each occurrence, independently hydrogen, $(C_1$-$C_6)$alkyl, trifluoromethyl, phenyl or monosubstituted $(C_1$-$C_6)$alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^c$, $S(O)_mR^c$, $C(O)OR^c$, $(C_3$-$C_7)$cycloalkyl, $-N(R^c)(R^c)$, $-C(O)N(R^c)(R^c)$, or R^a or R^b may independently be joined to one or both of R^7 or E (where E is other than O, S or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^a or R^b and the R^7 or E group, wherein the bridge contains 1 to 8 carbon atoms; or R^a and R^b may be joined to one another to form a $(C_3$-$C_7)$cycloalkyl;

R^c, for each occurrence, is independently hydrogen or $(C_1$-$C_6)$alkyl;

a and b are independently 0, 1, 2 or 3, with the proviso that if E is -O- or -S-, b is other than 0 or 1 and with the further proviso that if E is -CH=CH-, b is other than 0;

R^7 and R^8 are each independently hydrogen or optionally substituted $(C_1$-$C_6)$alkyl;

where the optionally substituted $(C_1$-$C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O-(C_1$-$C_6)$alkyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 $-O-C(O)(C_1$-$C_{10})$alkyl groups or 1 to 3 $(C_1$-$C_6)$alkoxy groups; or

R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, fluoro, hydroxy and $(C_1$-$C_5)$alkyl optionally independently substituted with 1-5 halo groups;

R^{11} is selected from the group consisting of $(C_1$-$C_5)$alkyl and phenyl optionally substituted with 1-3 substitutents each independently selected from the group consisting of $(C_1$-$C_5)$alkyl, halo and $(C_1$-$C_5)$alkoxy;

R^{12} is selected from the group consisting of $(C_1$-$C_5)$alkylsulfonyl, $(C_1$-$C_5)$alkanoyl and $(C_1$-$C_5)$alkyl where the alkyl portion is optionally independently substituted by 1-5 halo groups;

A^1 for each occurrence is independently selected from the group consisting of $(C_5$-$C_7)$cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-

membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, $(C_1$-$C_6)$alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-S(O)_2N(X^6)(X^6)$, $-N(X^6)S(O)_2$-phenyl, $-N(X^6)S(O)_2X^6$, $-CONX^{11}X^{12}$, $-S(O)_2NX^{11}X^{12}$, $-NX^6S(O)_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6S(O)_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted $(C_1$-$C_6)$alkyl;

the optionally substituted $(C_1$-$C_6)$alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, $(C_1$-$C_6)$alkoxycarbonyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 $(C_1$-$C_{10})$alkanoyloxy groups or 1 to 3 $(C_1$-$C_6)$alkoxy groups;

X^{12} is hydrogen, $(C_1$-$C_6)$alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, the X^{12} group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r$-L^1-$(CH_2)_r$-;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl or optionally substituted $(C_3$-$C_7)$cycloalkyl, where the optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^2 are

optionally independently substituted with -$S(O)_m(C_1$-$C_6)$alkyl, -$C(O)OX^3$, 1 to 5 halo groups or 1-3 OX^3 groups;

X^3 for each occurrence is independently hydrogen or $(C_1$-$C_6)$alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$halogenated alkyl, optionally substituted $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$-halogenated cycloalkyl, where optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^6 is optionally independently mono- or di-substituted with $(C_1$-$C_4)$alkyl, hydroxy, $(C_1$-$C_4)$alkoxy, carboxyl, $CONH_2$, -$S(O)_m(C_1$-$C_6)$alkyl, carboxylate $(C_1$-$C_4)$alkyl ester or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently $(C_1$-$C_6)$alkyl, the two $(C_1$-$C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 as a ring member;

X^7 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with hydroxy;

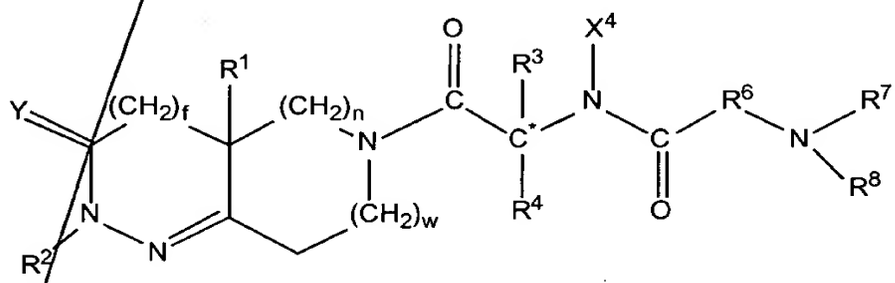
m for each occurrence is independently 0, 1 or 2;

with the provisos that:

1) X^6 and X^{12} cannot be hydrogen when attached to C(O) or $S(O)_2$ in the form $C(O)X^6$, $C(O)X^{12}$, $S(O)_2X^6$ or $S(O)_2X^{12}$; and

2) when R^6 is a bond then L is $N(X^2)$ and each r in the definition -$(CH_2)_r$-L-$(CH_2)_r$- is independently 2 or 3.

21. A combination of claim 20 wherein said GHS is a compound of the formula



a racemic-diastereomeric mixture or optical isomer of said compound or a pharmaceutically-acceptable salt and prodrug thereof,

wherein

f is 0;

n is 0 and w is 2, or n is 1 and w is 1, or n is 2 and w is 0;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 halogen;

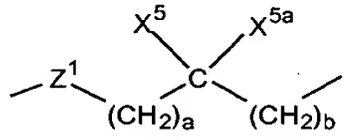
R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl, $-(C_1-C_5)$alkyl-$X^1-(C_0-C_5)$alkyl-A^1 or $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, -OC(O)-, -C(O)O-, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or -C≡C-;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl;

X^4 is hydrogen or $(C_1$-$C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is 

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted $(C_1$-$C_6)$alkyl;

the optionally substituted $(C_1$-$C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1$-$C_6)$alkyl, $-C(O)OX^2$, $(C_3$-$C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

R^7 and R^8 are independently hydrogen or optionally substituted $(C_1$-$C_6)$alkyl;

where the optionally substituted $(C_1$-$C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O-(C_1$-$C_6)$alkyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1$-$C_{10})$alkyl or 1 to 3 $(C_1$-$C_6)$alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 in the definition of R^1 is a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 in the definition of R^2, R^3, R^6, R^7 and R^8 is independently $(C_5$-$C_7)$cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8- membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6- membered ring,

optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitorgen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl or tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

where L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, -$S(O)_m$(C_1-C_6)alkyl, carboxylate (C_1-C_4)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^7)$ and each r in the definition -$(CH_2)_r$-L-$(CH_2)_r$- is independently 2 or 3.

22. A combination of claim 21 wherein the GHS is 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

23. A combination of claim 22 wherein the GHS is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, L-tartrate.

24. A combination of claim 21 wherein the GHS is 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

25. A combination of claim 24 wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide.

26. A combination of claim 21 wherein the GHS is 2-amino-N-{1(R)-benzyloxymethyl-2-[1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

27. A combination of claim 26 wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl)-2-methyl-propionamide.

28. A combination of claim 18 wherein said glucocorticoid is prednisone, betamethasone dipropionate, clobetasol, diflorasone diacetate, halobetasol propionate, amcinonide, desoximetasone, fluocinonide, halcinonide, betamethasone valerate, triamcinolone acetate, fluocinolone acetonide, flurandrenolide, hydrocortisone valerate, triamcinolone acetonide, hydrocortisone butyrate, alclometasone dipropionate, desonide, mometasone furoate, dexamethasone, hydrocortisone or methylprednisolone acetate.

29. A combination of claim 18 wherein said antimalarial is chloroquine, hydroxychloroquine, quinacrine or quinine.

30. A method of treating systemic lupus erythematosus in a patient which comprises administering to the patient

a) a combination of claim 18; or

b) a pharmaceutical composition comprising a GHS, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug; and a therapeutic agent selected from methotrexate, dapsone, a glucocorticoid or an antimalarial, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

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31 32. A kit comprising:

a) a first unit dosage form comprising a GHS, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent;

b) a second unit dosage form comprising a therapeutic agent selected from methotrexate, dapsone, a glucocorticoid or an antimalarial, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent; and

c) a container.

32 33. A method of treating inflammatory bowel disease in a patient which comprises administering to the patient an inflammatory bowel disease treating effective amount of a growth hormone secretagogue (GHS), a prodrug thereof or a pharmaceutically acceptable salt of said GHS or of said prodrug.

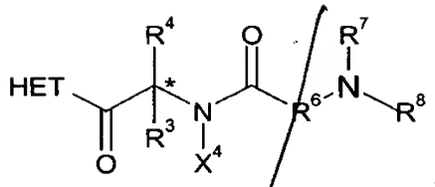
33 34. A method of claim 32 33 wherein the GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug is an orally active GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug.

34 35. A method of claim 33 34 wherein the GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug is orally administered.

35 36. A method of claim 34 33 wherein the GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug is a non-peptidyl GHS, prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug.

36 37. A method of claim 33 wherein the patient is a human.

37 38. A method of claim 36 wherein said GHS is a compound of the Formula I:



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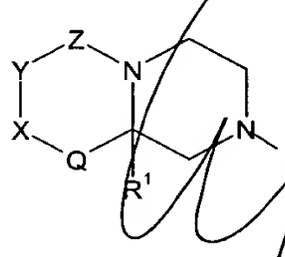
or a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer thereof, or a prodrug of such compound, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug,

wherein:

HET is a heterocyclic moiety selected from the group consisting of



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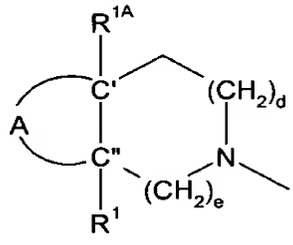

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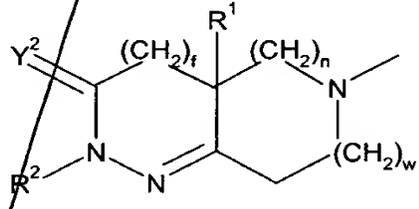

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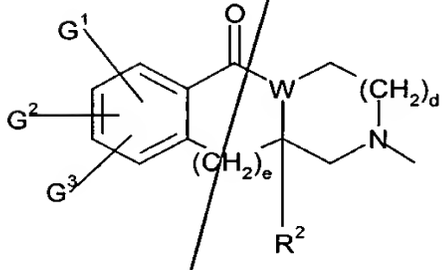
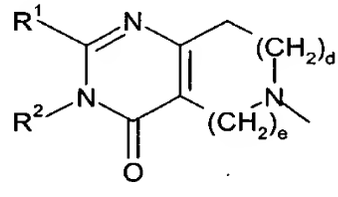


and



d is 0, 1 or 2;

e is 1 or 2;

f is 0 or 1;

n and w are 0, 1 or 2, provided that n and w cannot both be 0 at the same time;

Y^2 is oxygen or sulfur;

A is a divalent radical, where the left hand side of the radical as shown below is connected to C" and the right hand side of the radical as shown below is connected to C', selected from the group consisting of

$-NR^2-C(O)-NR^2-$, $-NR^2-S(O)_2-NR^2-$, $-O-C(O)-NR^2-$, $-NR^2-C(O)-O-$, $-C(O)-NR^2-C(O)-$, $-C(O)-NR^2-C(R^9R^{10})-$, $-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-O-C(O)-$, $-C(R^9R^{10})-O-C(R^9R^{10})-$, $-NR^2-C(O)-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-$, $-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(O)-O-$, $-C(O)-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-O-C(O)-$, $-NR^2-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-$, $-C(R^9R^{10})-NR^2-C(O)-O-$, $-C(R^9R^{10})-O-C(O)-NR^2$, $-C(R^9R^{10})-NR^2-C(O)-NR^2-$, $-NR^2-C(O)-O-C(R^9R^{10})-$, $-NR^2-C(O)-NR^2-C(R^9R^{10})-$, $-NR^2-S(O)_2-NR^2-C(R^9R^{10})-$, $-O-C(O)-NR^2-C(R^9R^{10})-$, $-C(O)-N=C(R^{11})-NR^2-$, $-C(O)-NR^2-C(R^{11})=N-$, $-C(R^9R^{10})-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-C(R^{11})=N-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-N(R^{12})-$, $-C(R^9R^{10})-NR^{12}-$, $-N=C(R^{11})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-S(O)_2-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-O-$, $-C(R^9R^{10})-S(O)_2-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-$, $-O-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-O-$, $-C(R^9R^{10})-C(O)-C(R^9R^{10})-$, $-C(O)-C(R^9R^{10})-C(R^9R^{10})-$ and $-C(R^9R^{10})-NR^2-S(O)_2-NR^2-$;

Q is a covalent bond or CH_2;

W is CH or N;

X is CR^9R^{10}, $C=CH_2$ or C=O;

Y is CR^9R^{10}, O or NR^2;

Z is C=O, C=S or $S(O)_2$;

G^1 is hydrogen, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, $-CONH_2$, $-(C_1-C_4)$alkyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkoxy optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkylthio, phenoxy, $-COO(C_1-C_4)$alkyl, N,N-di-(C_1-C_4)alkylamino, $-(C_2-C_6)$alkenyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_2-C_6)$alkynyl optionally independently

substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, -(C_3-C_6)cycloalkyl optionally independently substituted with one or more (C_1-C_4)alkyl groups, one or more halogens or one or more hydroxy groups, -(C_1-C_4)alkylamino carbonyl or di-(C_1-C_4)alkylamino carbonyl;

G^2 and G^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, -(C_1-C_4)alkyl optionally independently substituted with one to three halo groups and -(C_1-C_4)alkoxy optionally independently substituted with one to three halo groups;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)S(O)_2(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)S(O)_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t$-A^1, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t$-A^1, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t$-A^1, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)S(O)_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t$-A^1, -(C_1-C_{10})alkyl, $-(CH_2)_t$-A^1, $-(CH_2)_q$-(C_3-C_7)cycloalkyl, $-(CH_2)_q$-Y^1-(C_1-C_6)alkyl, $-(CH_2)_q$-Y^1-$(CH_2)_t$-A^1 or $-(CH_2)_q$-Y^1-$(CH_2)_t$-(C_3-C_7)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$-, -CH=CH-, -C≡C-, $-N(X^6)C(O)$-, $-C(O)NX^6$-, -C(O)O-, $-OC(O)N(X^6)$- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro groups or 1 or 2 (C_1-C_4)alkyl groups;

R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, (C_1-C_6)alkyl, phenyl(C_1-C_3)alkyl, pyridyl(C_1-C_3)alkyl, thiazolyl(C_1-C_3)alkyl and thienyl(C_1-C_3)alkyl, provided that R^{1A} is not F, Cl, Br or I when a heteroatom is vicinal to C";

R^2 is hydrogen, (C_1-C_8)alkyl, -(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl, -(C_1-C_4)alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxy, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 independently selected halo groups;

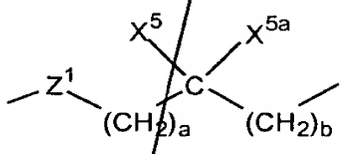
R^3 is selected from the group consisting of A^1, $(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_6)$alkyl-A^1, $-(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_0\text{-}C_5)$alkyl-A^1 and $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl-$(C_3\text{-}C_7)$cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 independently selected halo groups or 1, 2 or 3 independently selected $-OX^3$ groups;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_7)$cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form $(C_5\text{-}C_7)$cycloalkyl, $(C_5\text{-}C_7)$cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or $(C_1\text{-}C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are each independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3, A^1 and optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^2$, $(C_3\text{-}C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

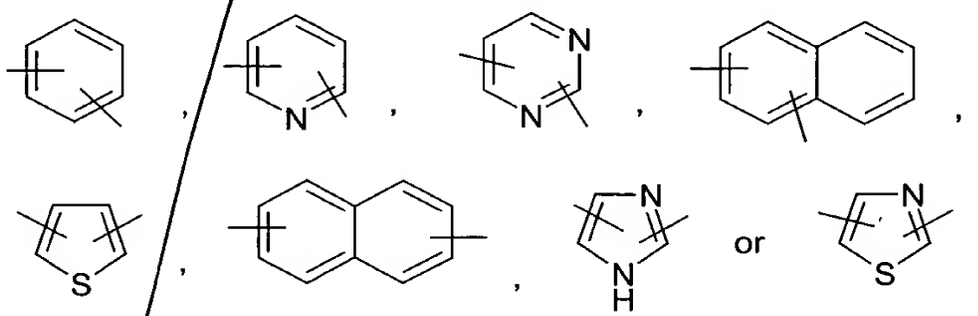
or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

or R^6 is -$(CR^aR^b)_a$-E-$(CR^aR^b)_b$-, where the -$(CR^aR^b)_a$- group is attached to the carbonyl carbon of the amide group of the compound of formula I and the -$(CR^aR^b)_b$ group is attached to the terminal nitrogen atom of the compound of formula I;

E is -O-, -S-, -CH=CH- or an aromatic moiety selected from



said aromatic moiety in the definition of E optionally substituted with up to three halo, hydroxy, -N(R^c)(R^c), (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

R^a and R^b are, for each occurrence, independently hydrogen, $(C_1$-$C_6)$alkyl, trifluoromethyl, phenyl or monosubstituted $(C_1$-$C_6)$alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^c$, $S(O)_mR^c$, $C(O)OR^c$, $(C_3$-$C_7)$cycloalkyl, $-N(R^c)(R^c)$, $-C(O)N(R^c)(R^c)$, or R^a or R^b may independently be joined to one or both of R^7 or E (where E is other than O, S or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^a or R^b and the R^7 or E group, wherein the bridge contains 1 to 8 carbon atoms; or R^a and R^b may be joined to one another to form a $(C_3$-$C_7)$cycloalkyl;

R^c, for each occurrence, is independently hydrogen or $(C_1$-$C_6)$alkyl;

a and b are independently 0, 1, 2 or 3, with the proviso that if E is -O- or -S-, b is other than 0 or 1 and with the further proviso that if E is -CH=CH-, b is other than 0;

R^7 and R^8 are each independently hydrogen or optionally substituted $(C_1$-$C_6)$alkyl;

where the optionally substituted $(C_1$-$C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O-(C_1$-$C_6)$alkyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 $-O-C(O)(C_1$-$C_{10})$alkyl groups or 1 to 3 $(C_1$-$C_6)$alkoxy groups; or

R^7 and R^8 can be taken together to form $-(CH_2)_r$-L-$(CH_2)_r$-;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, fluoro, hydroxy and $(C_1$-$C_5)$alkyl optionally independently substituted with 1-5 halo groups;

R^{11} is selected from the group consisting of $(C_1$-$C_5)$alkyl and phenyl optionally substituted with 1-3 substitutents each independently selected from the group consisting of $(C_1$-$C_5)$alkyl, halo and $(C_1$-$C_5)$alkoxy;

R^{12} is selected from the group consisting of $(C_1$-$C_5)$alkylsulfonyl, $(C_1$-$C_5)$alkanoyl and $(C_1$-$C_5)$alkyl where the alkyl portion is optionally independently substituted by 1-5 halo groups;

A^1 for each occurrence is independently selected from the group consisting of $(C_5$-$C_7)$cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-

membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-S(O)_2N(X^6)(X^6)$, $-N(X^6)S(O)_2$-phenyl, $-N(X^6)S(O)_2X^6$, $-CONX^{11}X^{12}$, $-S(O)_2NX^{11}X^{12}$, $-NX^6S(O)_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6S(O)_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 (C_1-C_{10})alkanoyloxy groups or 1 to 3 (C_1-C_6)alkoxy groups;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, the X^{12} group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are

optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halo groups or 1-3 OX^3 groups;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenated cycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently mono- or di-substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, carboxylate (C_1-C_4)alkyl ester or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 as a ring member;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxy;

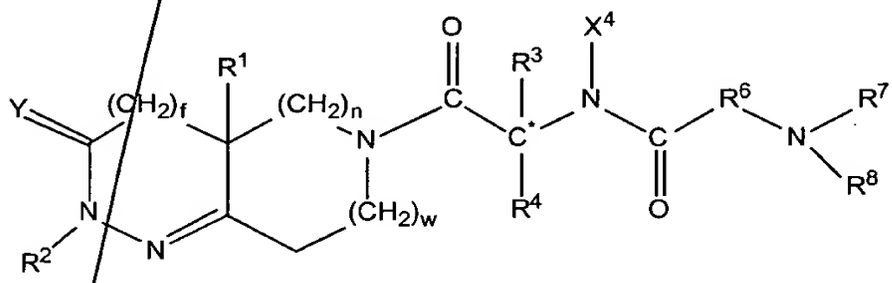
m for each occurrence is independently 0, 1 or 2;

with the provisos that:

1) X^6 and X^{12} cannot be hydrogen when attached to C(O) or $S(O)_2$ in the form $C(O)X^6$, $C(O)X^{12}$, $S(O)_2X^6$ or $S(O)_2X^{12}$; and

2) when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

39. A method of claim 38 wherein said GHS is a compound of the formula



a racemic-diastereomeric mixture or optical isomer of said compound or a pharmaceutically-acceptable salt or prodrug thereof,

wherein

f is 0;

n is 0 and w is 2, or n is 1 and w is 1, or n is 2 and w is 0;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 halogen;

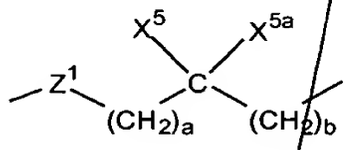
R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl, $-(C_1-C_5)$alkyl-$X^1-(C_0-C_5)$alkyl-A^1 or $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, -OC(O)-, -C(O)O-, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or -C≡C-;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl;

X^4 is hydrogen or $(C_1\text{-}C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^2$, $(C_3\text{-}C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

R^7 and R^8 are independently hydrogen or optionally substituted $(C_1\text{-}C_6)$alkyl;

where the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O\text{-}(C_1\text{-}C_6)$alkyl, $-S(O)_m(C_1\text{-}C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O\text{-}C(O)(C_1\text{-}C_{10})$alkyl or 1 to 3 $(C_1\text{-}C_6)$alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r\text{-}L\text{-}(CH_2)_r$-;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 in the definition of R^1 is a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 in the definition of R^2, R^3, R^6, R^7 and R^8 is independently $(C_5\text{-}C_7)$cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8- membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6- membered ring,

optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitorgen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl or tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

where L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$halogenated alkyl, optionally substituted $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$-halogenatedcycloalkyl, where optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 $(C_1$-$C_4)$alkyl, hydroxyl, $(C_1$-$C_4)$alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1$-$C_6)$alkyl, carboxylate $(C_1$-$C_4)$alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently $(C_1$-$C_6)$alkyl, the two $(C_1$-$C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r$-L-$(CH_2)_r$- is independently 2 or 3.

~~40~~ 39. A method of claim ~~39~~ 38 wherein the GHS is 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

~~41~~ 40. A method of claim ~~40~~ 39 wherein the GHS is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, L-tartrate.

~~42~~ 41. A method of claim 39 wherein the GHS is 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

42
~~43~~. A method of claim 40 wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide.

43
~~44~~. A method of claim 39 wherein the GHS is 2-amino-N-{1(R)-benzyloxymethyl-2-[1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

44 43
~~45~~. A method of claim ~~44~~ wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl)-2-methyl-propionamide.

45
~~46~~. A method of claim 33 wherein said inflammatory bowel disease is Crohn's disease.

46
~~47~~. A method of claim 33 wherein said inflammatory bowel disease is ulcerative colitis.

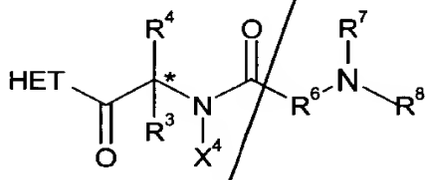
47
~~48~~. A method of claim 33 which further comprises administering a recombinant growth hormone or an additional GHS selected from the group consisting of GHRP-6, GHRP-1, GHRP-2, growth hormone releasing factor and an analog of growth hormone releasing factor.

48
~~49~~. A combination comprising a GHS, a prodrug thereof or pharmaceutically acceptable salt thereof or of said prodrug and a second therapeutic agent selected from prednisone, sulfasalazine, mesalamine and olsalazine, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

49
~~50~~. A pharmaceutical composition comprising a combination of claim ~~49~~ 48 and a pharmaceutically acceptable carrier, vehicle or diluent.

50

51. A combination of claim 49 wherein said GHS is a compound of the Formula I:

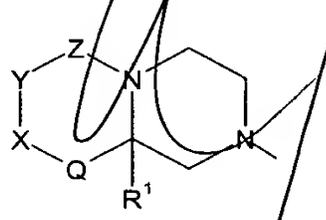


I

or a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer thereof, or a prodrug of such compound, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug,

wherein:

HET is a heterocyclic moiety selected from the group consisting of



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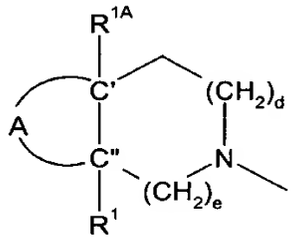

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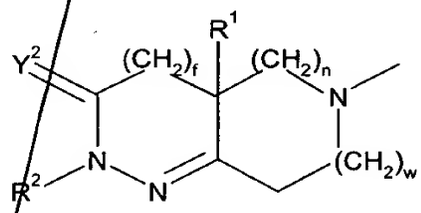

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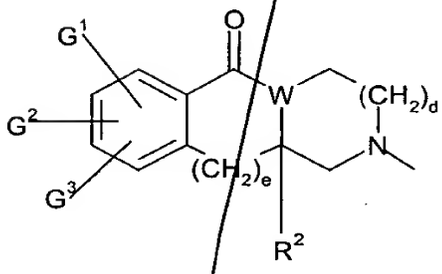

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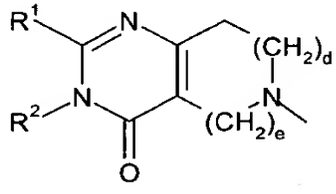


d is 0, 1 or 2;

e is 1 or 2;

f is 0 or 1;

n and w are 0, 1 or 2, provided that n and w cannot both be 0 at the same time;

Y^2 is oxygen or sulfur;

A is a divalent radical, where the left hand side of the radical as shown below is connected to C" and the right hand side of the radical as shown below is connected to C', selected from the group consisting of

$-NR^2-C(O)-NR^2-$, $-NR^2-S(O)_2-NR^2-$, $-O-C(O)-NR^2-$, $-NR^2-C(O)-O-$, $-C(O)-NR^2-C(O)-$, $-C(O)-NR^2-C(R^9R^{10})-$, $-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-O-C(O)-$, $-C(R^9R^{10})-O-C(R^9R^{10})-$, $-NR^2-C(O)-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-$, $-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(O)-O-$, $-C(O)-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-$, $-S(O)_2-NR^2-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-O-C(O)-$, $-NR^2-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-S(O)_2-C(R^9R^{10})-C(R^9R^{10})-$, $-O-C(O)-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-$, $-C(R^9R^{10})-NR^2-C(O)-O-$, $-C(R^9R^{10})-O-C(O)-NR^2$, $-C(R^9R^{10})-NR^2-C(O)-NR^2-$, $-NR^2-C(O)-O-C(R^9R^{10})-$, $-NR^2-C(O)-NR^2-C(R^9R^{10})-$, $-NR^2-S(O)_2-NR^2-C(R^9R^{10})-$, $-O-C(O)-NR^2-C(R^9R^{10})-$, $-C(O)-N=C(R^{11})-NR^2-$, $-C(O)-NR^2-C(R^{11})=N-$, $-C(R^9R^{10})-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-C(R^9R^{10})-$, $-C(O)-O-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-C(R^{11})=N-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-N(R^{12})-$, $-C(R^9R^{10})-NR^{12}-$, $-N=C(R^{11})-NR^2-C(O)-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-S(O)_2-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-C(O)-O-$, $-C(R^9R^{10})-S(O)_2-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-S(O)_2-$, $-O-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-O-$, $-C(R^9R^{10})-C(O)-C(R^9R^{10})-$, $-C(O)-C(R^9R^{10})-C(R^9R^{10})-$ and $-C(R^9R^{10})-NR^2-S(O)_2-NR^2-$;

Q is a covalent bond or CH_2;

W is CH or N;

X is CR^9R^{10}, $C=CH_2$ or C=O;

Y is CR^9R^{10}, O or NR^2;

Z is C=O, C=S or $S(O)_2$;

G^1 is hydrogen, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, $-CONH_2$, $-(C_1-C_4)$alkyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkoxy optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkylthio, phenoxy, $-COO(C_1-C_4)$alkyl, N,N-di-(C_1-C_4)alkylamino, $-(C_2-C_6)$alkenyl optionally independently substituted with one or more phenyl, one or more

halogens or one or more hydroxy groups, -(C_2-C_6)alkynyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, -(C_3-C_6)cycloalkyl optionally independently substituted with one or more (C_1-C_4)alkyl groups, one or more halogens or one or more hydroxy groups, -(C_1-C_4)alkylamino carbonyl or di-(C_1-C_4)alkylamino carbonyl;

G^2 and G^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, -(C_1-C_4)alkyl optionally independently substituted with one to three halo groups and -(C_1-C_4)alkoxy optionally independently substituted with one to three halo groups;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)S(O)_2(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)S(O)_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t$-A^1, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t$-A^1, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t$-$A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t$-A^1, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)S(O)_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t$-A^1, -(C_1-C_{10})alkyl, $-(CH_2)_t$-A^1, $-(CH_2)_q$-(C_3-C_7)cycloalkyl, $-(CH_2)_q$-Y^1-(C_1-C_6)alkyl, $-(CH_2)_q$-Y^1-$(CH_2)_t$-A^1 or $-(CH_2)_q$-Y^1-$(CH_2)_t$-(C_3-C_7)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$-, -CH=CH-, -C≡C-, $-N(X^6)C(O)$-, $-C(O)NX^6$-, -C(O)O-, $-OC(O)N(X^6)$- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro groups or 1 or 2 (C_1-C_4)alkyl groups;

R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, (C_1-C_6)alkyl, phenyl(C_1-C_3)alkyl, pyridyl(C_1-C_3)alkyl, thiazolyl(C_1-C_3)alkyl and thienyl(C_1-C_3)alkyl, provided that R^{1A} is not F, Cl, Br or I when a heteroatom is vicinal to C";

R^2 is hydrogen, (C_1-C_8)alkyl, -(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl, -(C_1-C_4)alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxy, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 independently selected halo groups;

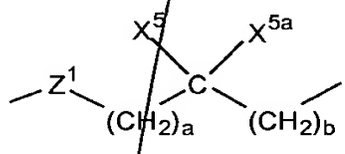
R^3 is selected from the group consisting of A^1, $(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_6)$alkyl-A^1, $-(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl, $-(C_1\text{-}C_5)$alkyl-X^1-$(C_0\text{-}C_5)$alkyl-A^1 and $-(C_1\text{-}C_5)$alkyl-X^1-$(C_1\text{-}C_5)$alkyl-$(C_3\text{-}C_7)$cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 independently selected halo groups or 1, 2 or 3 independently selected $-OX^3$ groups;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_7)$cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form $(C_5\text{-}C_7)$cycloalkyl, $(C_5\text{-}C_7)$cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or $(C_1\text{-}C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are each independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3, A^1 and optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^2$, $(C_3\text{-}C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

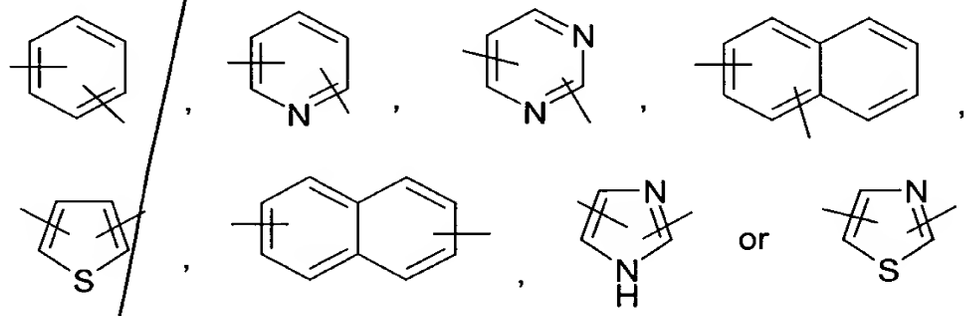
or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

or R^6 is $-(CR^aR^b)_a-E-(CR^aR^b)_b-$, where the $-(CR^aR^b)_a-$ group is attached to the carbonyl carbon of the amide group of the compound of formula I and the $-(CR^aR^b)_b$ group is attached to the terminal nitrogen atom of the compound of formula I;

E is -O-, -S-, -CH=CH- or an aromatic moiety selected from



said aromatic moiety in the definition of E optionally substituted with up to three halo, hydroxy, $-N(R^c)(R^c)$, (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

R^a and R^b are, for each occurrence, independently hydrogen, $(C_1$-$C_6)$alkyl, trifluoromethyl, phenyl or monosubstituted $(C_1$-$C_6)$alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^c$, $S(O)_mR^c$, $C(O)OR^c$, $(C_3$-$C_7)$cycloalkyl, $-N(R^c)(R^c)$, $-C(O)N(R^c)(R^c)$, or R^a or R^b may independently be joined to one or both of R^7 or E (where E is other than O, S or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^a or R^b and the R^7 or E group, wherein the bridge contains 1 to 8 carbon atoms; or R^a and R^b may be joined to one another to form a $(C_3$-$C_7)$cycloalkyl;

R^c, for each occurrence, is independently hydrogen or $(C_1$-$C_6)$alkyl;

a and b are independently 0, 1, 2 or 3, with the proviso that if E is -O- or -S-, b is other than 0 or 1 and with the further proviso that if E is -CH=CH-, b is other than 0;

R^7 and R^8 are each independently hydrogen or optionally substituted $(C_1$-$C_6)$alkyl;

where the optionally substituted $(C_1$-$C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O$-$(C_1$-$C_6)$alkyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 $-O$-$C(O)(C_1$-$C_{10})$alkyl groups or 1 to 3 $(C_1$-$C_6)$alkoxy groups; or

R^7 and R^8 can be taken together to form $-(CH_2)_r$-L-$(CH_2)_r$-;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, fluoro, hydroxy and $(C_1$-$C_5)$alkyl optionally independently substituted with 1-5 halo groups;

R^{11} is selected from the group consisting of $(C_1$-$C_5)$alkyl and phenyl optionally substituted with 1-3 substitutents each independently selected from the group consisting of $(C_1$-$C_5)$alkyl, halo and $(C_1$-$C_5)$alkoxy;

R^{12} is selected from the group consisting of $(C_1$-$C_5)$alkylsulfonyl, $(C_1$-$C_5)$alkanoyl and $(C_1$-$C_5)$alkyl where the alkyl portion is optionally independently substituted by 1-5 halo groups;

A^1 for each occurrence is independently selected from the group consisting of $(C_5$-$C_7)$cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-

membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-S(O)_2N(X^6)(X^6)$, $-N(X^6)S(O)_2$-phenyl, $-N(X^6)S(O)_2X^6$, $-CONX^{11}X^{12}$, $-S(O)_2NX^{11}X^{12}$, $-NX^6S(O)_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6S(O)_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 (C_1-C_{10})alkanoyloxy groups or 1 to 3 (C_1-C_6)alkoxy groups;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, the X^{12} group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are

optionally independently substituted with -$S(O)_m(C_1$-$C_8)$alkyl, -$C(O)OX^3$, 1 to 5 halo groups or 1-3 OX^3 groups;

X^3 for each occurrence is independently hydrogen or $(C_1$-$C_6)$alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$halogenated alkyl, optionally substituted $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$-halogenated cycloalkyl, where optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^6 is optionally independently mono- or di-substituted with $(C_1$-$C_4)$alkyl, hydroxy, $(C_1$-$C_4)$alkoxy, carboxyl, $CONH_2$, -$S(O)_m(C_1$-$C_6)$alkyl, carboxylate $(C_1$-$C_4)$alkyl ester or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently $(C_1$-$C_6)$alkyl, the two $(C_1$-$C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 as a ring member;

X^7 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with hydroxy;

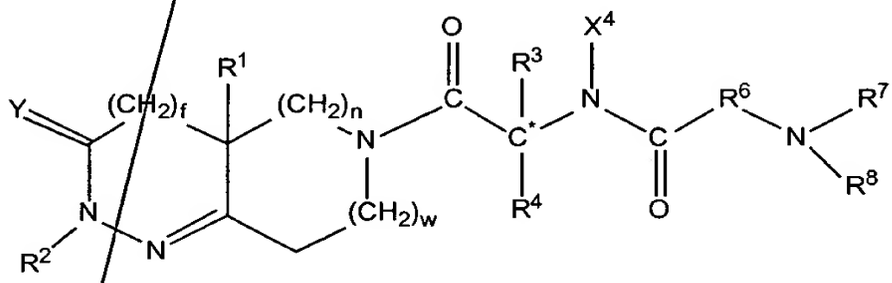
m for each occurrence is independently 0, 1 or 2;

with the provisos that:

1) X^6 and X^{12} cannot be hydrogen when attached to C(O) or $S(O)_2$ in the form $C(O)X^6$, $C(O)X^{12}$, $S(O)_2X^6$ or $S(O)_2X^{12}$; and

2) when R^6 is a bond then L is $N(X^2)$ and each r in the definition -$(CH_2)_r$-L-$(CH_2)_r$- is independently 2 or 3.

51 ~~52~~. A combination of claim 50 wherein said GHS is a compound of the formula



a racemic-diastereomeric mixture or optical isomer of said compound or a pharmaceutically-acceptable salt and prodrug thereof,

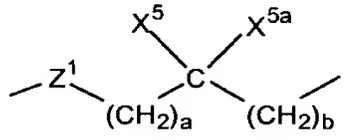
wherein

f is 0;

n is 0 and w is 2, or n is 1 and w is 1, or n is 2 and w is 0;

Y is oxygen or sulfur;

X^4 is hydrogen or $(C_1\text{-}C_6)$alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^2$, $(C_3\text{-}C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

R^7 and R^8 are independently hydrogen or optionally substituted $(C_1\text{-}C_6)$alkyl;

where the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O\text{-}(C_1\text{-}C_6)$alkyl, $-S(O)_m(C_1\text{-}C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O\text{-}C(O)(C_1\text{-}C_{10})$alkyl or 1 to 3 $(C_1\text{-}C_6)$alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r\text{-}L\text{-}(CH_2)_r$-;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 in the definition of R^1 is a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 in the definition of R^2, R^3, R^6, R^7 and R^8 is independently $(C_5\text{-}C_7)$cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8- membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6- membered ring,

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 halogen;

R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl, $-(C_1-C_5)$alkyl-$X^1-(C_0-C_5)$alkyl-A^1 or $-(C_1-C_5)$alkyl-$X^1-(C_1-C_5)$alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, -OC(O)-, -C(O)O-, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or -C≡C-;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl;

optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitorgen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl or tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

where L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, carboxylate (C_1-C_4)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

53. A combination of claim 52 wherein the GHS is 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

54. A combination of claim 53 wherein the GHS is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, L-tartrate.

55. A combination of claim 52 wherein the GHS is 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

55 54
~~56~~. A combination of claim ~~55~~ wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide.

56
~~57~~. A combination of claim 52 wherein the GHS is 2-amino-N-{1(R)-benzyloxymethyl-2-[1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug.

57 56
~~58~~. A combination of claim ~~57~~ wherein the GHS is the (L)-(+)-tartaric acid salt of 2-amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl)-2-methyl-propionamide.

58
~~59~~. A method of treating inflammatory bowel disease in a patient which comprises administering to the patient

a) a combination of claim 49; or

b) a pharmaceutical composition comprising a GHS, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug; and an agent selected from prednisone, sulfasalazine, mesalamine and olsalazine, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

59 58
~~60~~. A method of claim ~~59~~ wherein said inflammatory bowel disease is Crohn's disease.

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~~61~~. A method of claim 59 wherein said inflammatory bowel disease is ulcerative colitis.

61
~~62~~. A kit comprising:

a) a first unit dosage form comprising a GHS, a prodrug thereof or a pharmaceutically acceptable salt of said GHS or said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent;

b) a second unit dosage form comprising an agent selected from prednisone, sulfasalazine, mesalamine and olsalazine, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent; and

c) a container.